Investigation of Focused Cardiac Ultrasound in the Emergency Room for Differentiation of Respiratory and Cardiac Causes of Respiratory Distress in Dogs

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Running title: Emergency Focused Cardiac Ultrasound

Abbreviations:

C	Cardiac
CI	Confidence interval
ECC	Emergency and critical care
FOCUS	Focused cardiac ultrasound
LA:Ao	Ratio of left atrial to aortic root diameter
LVIDDN	Left ventricular internal dimension in diastole, normalized for body weight
LVIDSN	Left ventricular internal dimension in systole, normalized for body weight
NC	Non-cardiac
PE	Physical examination
SBP	Systolic blood pressure

TFAST	Thoracic focused assessment with sonography for trauma
VHS	Vertebral heart scale

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Abstract

Objective: To determine whether focused cardiac ultrasound (FOCUS) performed by emergency and critical care (ECC) specialists or residents in training improves differentiation of cardiac (C) vs. non-cardiac (NC) causes of respiratory distress in dogs compared to medical history and physical examination alone.

Design: Prospective cohort study (May 2014 - February 2016).

Setting: University hospital.

Animals: Thirty-eight dogs presenting with respiratory distress.

Interventions: FOCUS.

Measurements and Main Results: Medical history, physical examination, and FOCUS were obtained at presentation. ECC clinicians, blinded to any radiographic or echocardiographic data, categorized each patient (C vs. NC) before and after FOCUS. Thoracic radiography (within 3 hours) and echocardiography (within 24 hours) were performed. Percent agreement was calculated against a reference diagnosis that relied on agreement of a board-certified cardiologist and ECC clinician with access to all diagnostic test results. Reference diagnosis included 22 dogs with cardiac and 13 dogs with non-cardiac causes of respiratory distress. In 3 dogs a reference diagnosis was not established. Prior to FOCUS, positive and negative percent agreement to detect cardiac causes was 90.9% (95% CI, 70.8-98.9%) and 53.9% (25.1-80.8%), respectively. Overall agreement occurred in 27/35 dogs (77.1%). Two C and 6 NC cases were incorrectly categorized. Following FOCUS, positive and negative percent agreement to detect cardiac causes was 95.5% (77.2-99.9%) and 69.2% (38.6-90.9%), respectively. Overall agreement occurred in 30/35 dogs (85.7%). Three dogs with discrepant pre-FOCUS diagnoses were correctly re-categorized post-FOCUS. One C and 4 NC cases remained incorrectly categorized. No correctly categorized dogs were incorrectly re-categorized following FOCUS. The proportions of dogs correctly classified pre- vs. post-FOCUS were not significantly different (P=0.25).

Conclusions: FOCUS did not significantly improve differentiation of C vs NC causes of respiratory distress compared to medical history and physical examination alone.

Keywords: diagnostic testing, canine, echocardiography

Introduction

Respiratory distress is a common reason for emergency veterinary visits in dogs and may result from a wide variety of underlying disease processes, including congestive heart failure, laryngeal paralysis, neoplasia, pulmonary thromboembolism and pneumonia.(1-3) Early and accurate diagnosis is essential for optimal therapy to be initiated in a timely manner. Initially, it is important to distinguish congestive heart failure from primary respiratory diseases since therapies and diagnostic strategies can differ significantly. However, it is often difficult to differentiate cardiac (C) from non-cardiac (NC) causes of respiratory distress on the basis of clinical history and physical examination (PE) alone.(4) Many patients require supplementary oxygen and may not be sufficiently stable to tolerate diagnostic tests, such as radiography and echocardiography.

In human emergency rooms, focused cardiac ultrasound (FOCUS) by emergency and critical care (ECC) clinicians is an established method for the time-sensitive assessment of dyspneic patients.(5) FOCUS is a 2-dimensional ultrasound exam intended to be problem-oriented and limited in scope, ideally to answer binary "yes/ no" questions (e.g., is there cardiac chamber enlargement, is there pleural effusion, etc.).(6) FOCUS in dyspneic human patients includes an evaluation of overall cardiac chamber size and function, volume status, presence or absence of pericardial or pleural effusion, and acute right-sided cardiomegaly, which may suggest pulmonary thromboembolism (5, 7) The usefulness of FOCUS in the identification of pulseless electrical activity has also been described.(8) FOCUS has been shown to be superior to physical examination alone in the identification of cardiac disease in human patients, regardless of the experience level of the person performing the examination.(9-11) However, FOCUS is not intended to supplant an eventual comprehensive echocardiogram, which is strongly indicated in all people presenting with acute respiratory distress.(5)

The use of problem-orientated thoracic ultrasonography has become commonplace in veterinary emergency practice in recent years. Thoracic focused assessment with sonography for trauma (TFAST) is a widely-used technique which has been shown to be useful in the identification of pleural and pericardial fluid.(12) Ultrasonography of the lungs identifies changes consistent with interstitial edema. The sensitivity of this test for identification of left-sided congestive heart failure is high but the specificity may be affected by false positives associated with other severe interstitial or alveolar lung diseases, such as pneumonia.(13, 14) Previously, ECC clinicians were able to identify pericardial and pleural effusion and differentiate left atrial enlargement from a normal left atrial size following a prescribed FOCUS training course.(15) However, the clinical utility of FOCUS to differentiate cardiac from non-cardiac causes of respiratory distress has not been investigated in veterinary patients. We hypothesized that FOCUS examinations performed by ECC clinicians would improve overall agreement in distinguishing C vs. NC causes of respiratory distress in dogs compared to a diagnosis made on the basis of medical history and PE alone.

Materials and Methods

The study protocol was approved by the University of Pennsylvania animal use and care committee and informed owner consent was obtained. ECC specialists and residents in training underwent a 3-hour structured training program in FOCUS, based on previously described methods.(15) Briefly, a 60-minute didactic presentation was followed by 2 hours of practical hands-on training. The goals of the training program included recognition of basic cardiac structure and function, detection of pericardial or pleural effusion, and quantitative measurement of left atrial and aortic root diameters from right parasternal short axis views, in order to calculate their ratio (LA:Ao).(16)

Dogs that were presented to the Matthew J. Ryan Hospital of the University of Pennsylvania for evaluation of respiratory distress requiring supplemental oxygen therapy were prospectively recruited. Exclusion criteria included intravenous fluid therapy within 72 hours of presentation, known trauma, and severe systemic disease precluding participation. Failure to perform thoracic radiography within 3 hours of presentation or echocardiography within 24 hours of presentation also resulted in exclusion from the study. The ECC clinician performing FOCUS was blinded to the results of any diagnostic tests performed prior to their evaluation (e.g., radiographs performed by the primary veterinarian prior to referral). The ECC clinician obtained a medical history and performed a physical examination, following which they completed a standardized case report form and categorized the cause of respiratory distress as either cardiac (C) or non-cardiac (NC). The clinician then performed the FOCUS, during which the dog was positioned to sit or stand, and supplementary oxygen was administered. Right parasternal short-axis views were obtained at the level of the papillary muscles and at the level of the left atrium. A post-FOCUS standardized case report form was then completed, and a post-FOCUS diagnosis of C or NC was again recorded. Recorded data also included quantitative assessment of LA:Ao, the presence or absence of pleural and pericardial effusion and a subjective assessment of left and right ventricular size and function. The study design is summarized in Figure 1. Systolic blood pressure (SBP) was measured by Doppler sphygmomanometry,[a] according to a previously published protocol.(17) The diameter of the limb to be used was measured and the inflatable pressure cuff of width closest to 40% of the antebrachial circumference chosen. Thoracic radiography was performed subsequent to the FOCUS examination and within 3 hours of presentation. Vertebral heart scale (VHS) was calculated by a single observer (MJH), as previously described.(18) Echocardiographic examinations [b] were performed within 24 hours of presentation by a board-certified cardiologist or supervised resident in training, using standard techniques. Dogs were placed in right and then left lateral recumbency on an ultrasound examination table. Standard imaging planes were digitally stored. LA:Ao was measured from the right parasternal short axis view.(16) Two dimensional measurements of the left ventricle from the right parasternal short axis view were used to derive normalized left ventricular end-systolic diameter (LVIDSN) and left ventricular end-diastolic diameter (LVIDDN) using previously described formulae.(19) Any additional diagnostic testing was performed at the discretion of the attending clinician.

The accuracy of the ECC clinicians' diagnoses, both prior to and following the FOCUS examination, was calculated against a reference diagnosis, determined on the basis of consensus between a board-certified cardiologist and a board-certified ECC specialist, who had access to the results of all diagnostic tests and response to therapy and were blinded to FOCUS results from other clinicians.

Statistical Methods

The study design was based on the *a priori* hypothesis that FOCUS would improve overall percent agreement by 20%, from a pre-FOCUS value of 65% to a post-FOCUS value of 85%, with a power of 80% and alpha of 0.05. A difference of 20% was empirically chosen to represent a clinically meaningful improvement. Statistical analyses were performed using commercially available software.[c] Data were assessed graphically and by use of the Shapiro-

Wilk test for normality. Means and standard deviations or standard errors of the mean were used to provide descriptive statistics for normally distributed continuous variables. Medians and ranges were used to provide descriptive statistics for non-normally distributed continuous variables. Comparisons of continuous variables between groups were performed using Student's *t*-tests or Mann-Whitney U-tests, as appropriate. Comparisons of proportions between groups at baseline were performed using Fisher's exact test. Agreement between the FOCUS and reference-based diagnosis was determined by construction of 2x2 tables and calculating the positive, negative, and overall percent agreement.[d] Specifically, positive percent agreement was the proportion of cases categorized as C by both the FOCUS-based and reference-based methods over the number of C cases diagnosed by the reference method. Negative percent agreement was the proportion of cases diagnosed as NC by both the FOCUS-based and reference-based methods over the number of NC cases diagnosed by the reference method. Overall percent agreement was the total number of concordant cases over the number of total cases. The proportions of pre- vs. post-FOCUS diagnoses that were in agreement with the reference diagnosis were compared using McNemar's test. The level of agreement between the FOCUS and reference diagnosis was further examined by calculation of Cohen's kappa. Levels of agreement based on kappa values were prespecified as follows: poor, 0.00-0.20; slight 0.21-0.40; moderate, 0.41-0.60; good, 0.61-0.80; very good, 0.81-1.00.(20) Statistical significance was set at $P < 0.05$.

Results

Thirty-eight dogs were recruited to the study. In 3 dogs, a reference diagnosis could not be made with confidence or agreement between the specialists and these cases were removed from further analysis. Of the remaining 35 dogs, mixed breeds were most frequently represented (n =

10), followed by cavalier King Charles spaniels (n = 5), Yorkshire terriers (n = 3), 2 each of Bulldog, Shih Tzu and toy poodle and 1 each of Boston terrier, Chihuahua, dachshund, great Dane, Italian greyhound, Japanese chin, Labrador retriever, miniature schnauzer, Pomeranian, rat terrier and Shetland sheepdog. The reference diagnosis was C in 22 dogs and NC in 13 dogs. Summary statistics of the patient groups are shown in Table 1. Dogs in the C group were more likely to have a heart murmur and greater VHS, LA:Ao on both FOCUS examination and echocardiography, LVIDDN and LVIDSN (all $P < 0.05$).

Twenty-one cases were examined by ECC residents and 14 cases by ECC faculty. The pre-FOCUS positive percent agreement between the ECC clinician and reference diagnosis was 90.9% (20/22 dogs) and negative percent agreement was 53.8% (7/13 dogs) with an overall percent agreement of 77.1% (27/ 35 dogs). Overall percent agreement achieved by faculty vs. residents was not statistically different (faculty, 64.3% [9/14 dogs] vs. residents, 85.7% [18/21 dogs]; P=0.139). The level of agreement between the ECC clinician and the reference diagnosis was moderate (kappa, 0.478 [SEM, 0.163]).

Following the FOCUS examination, positive and negative percent agreement was 95.5% (21/22 dogs) and 69.2% (9/13 dogs), respectively, with an overall percent agreement of 85.7% (30/35 dogs). Overall percent agreement achieved by faculty vs. residents was not significantly different (faculty, 78.6% [11/14 dogs] vs. residents, 90.5% [19/21 dogs]; P=0.324). The level of agreement between the ECC clinician and the reference diagnosis post-FOCUS was good (kappa: 0.679 [SE, 0.166]). Three dogs with discrepant pre-FOCUS diagnoses were correctly re-categorized post-FOCUS, including 1 dog whose cause was C and 2 dogs whose cause was NC. One C and 4 NC cases remained incorrectly categorized post-FOCUS. Dogs in the NC group judged to have LA enlargement on the FOCUS exam were more likely to be incorrectly categorized (P = 0.021). No dog correctly categorized prior to FOCUS was incorrectly re-categorized following the examination. Post-FOCUS, neither the overall percent agreement nor the kappa value was significantly different from pre-FOCUS values (P=0.25 and P=0.39), respectively. The agreement within the C and NC groups before and after FOCUS is summarized in Figure 2.

Discussion

The results of this study indicate that ECC clinicians were able to differentiate C from NC causes of respiratory distress in a high percentage of cases on the basis of medical history and PE. Although positive, negative, and overall percent agreement increased following FOCUS, the change was not statistically significant. Nevertheless, for the 3 dogs whose discrepant diagnoses were changed post-FOCUS, initiation of appropriate therapy was facilitated, and no dog that was correctly categorized pre-FOCUS was incorrectly re-categorized post-FOCUS.

Differentiating cause of respiratory distress in dogs can be a diagnostic challenge in clinical practice. Indeed, in the current study, board certified-specialists were not able to arrive at a reference diagnosis in 3 dogs despite access to results of all available diagnostic tests and response to therapy. To the authors' knowledge, the ability of ECC clinicians to distinguish cause of respiratory distress in dogs based solely on medical history and PE has not been previously reported. In the current study, the percentage of cases in agreement with the reference diagnosis based on history and PE was unexpectedly high. The reason for this is unknown, but might be related to the tertiary nature of the study center where some cases have a medical history that may include previous episodes of C or NC causes of respiratory signs. Generally, diagnostic tests have greatest clinical utility in instances wherein the pre-test probability of a condition is close to 50% (e.g. is very uncertain), and in instances wherein confidence of diagnosis is high, additional diagnostic testing, including FOCUS, might not add substantial gain.(21) Future studies might investigate use of FOCUS in patients with respiratory distress that specifically present the ECC clinician with a high degree of pre-FOCUS uncertainty. Following FOCUS, 85.7% of cases were in agreement with the reference diagnosis, a percentage that is similar to what was anticipated. A larger number of dogs in group NC vs. those in group C remained in disagreement. In these NC cases, a FOCUS finding of an enlarged LA:Ao due to concurrent (but asymptomatic) heart disease appears to have hindered re-categorization.

In agreement with studies investigating the use of FOCUS by physicians, there was no difference in diagnostic accuracy between faculty and residents(10), despite expectation that agreement might increase with experience. Future studies might choose to stratify examiners based on duration of emergency room experience as opposed to academic title, which might not account for faculty recently achieving diplomate status or residents with many years of previous work experience. Additionally, the current study was performed in a single academic center, in which the faculty trains the residents, and this may have increased the homogeneity of the results between examiners.

Use of FOCUS in the emergency room is one of several emerging trends in emergency medicine. The clinical utility of lung ultrasound(14) and natriuretic peptide testing(22) have been previously reported. Any single modality is unlikely to be uniformly optimal and future studies of a multi-modality approach combining FOCUS, lung ultrasound and NT-proBNP testing are appealing. However, the lack of availability of a point-of-care NT-proBNP assay for dogs limits the utility of this test in the emergency setting. FOCUS examination might also perform best in cases with pleural effusion, which hinders the utility of lung ultrasound. In cases in which FOCUS identifies heart enlargement, lung ultrasound could be used to assess the likelihood of pulmonary edema; and in cases with positive findings on lung ultrasound, FOCUS-based assessment of left heart size could help determine likelihood of pulmonary edema from heavy interstitial or alveolar disease of NC cause.

There are several important limitations to the current study. The study was restricted to a single academic emergency service in a busy urban environment and the findings may not be applicable to different emergency practices or personnel. FOCUS examinations were performed using a single ultrasound machine; the diagnostic quality of images obtained varies with both operator and equipment factors, and so the results may not be applicable to other ultrasound machines. Dogs with congestive heart failure formed the majority of cases, which is reflective of our hospital caseload, and the findings might not be applicable to different populations, in which NC disease may predominate. Echocardiography was frequently performed after the initiation of therapy, which might have influenced echocardiographic measurements and the subsequent reference diagnosis.

In conclusion, ECC clinicians are able to correctly categorize C and NC causes of respiratory distress on the basis of the combination of medical history, physical examination and FOCUS examination in the majority of dogs. Focused cardiac ultrasound by a trained ECC clinician did not significantly improve the overall agreement with a reference diagnosis compared to a diagnosis made on the basis of history and physical examination alone. Future studies in different patient populations and use of FOCUS in conjunction with other diagnostic modalities are of interest.

Footnotes

[a] Parks Medical Electronics Inc., Aloha, OR

[b] iE33, Royal Philips, Amsterdam, The Netherlands

[c] IBM SPSS Statistics 23.0, IBM Corporation, Armonk, NY

[d] U.S. Department of Health and Human Services, Food and Drug Administration. Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests. http://www.fda.gov/cdrh/osb/guidance/1620.pdf; accessed Feb 2018).

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Table 1: Characteristics of the cardiac and respiratory groups. The mean ± standard deviation is shown for normally distributed continuous variables. The median and ranges are shown for non-normally distributed continuous variables.

VHS, vertebral heart scale; LA:Ao ratio of left atrial to aortic diameter; LVIDDN, left ventricular end-diastolic diameter normalized for body weight; LVIDSN, left ventricular end-systolic diameter normalized for body weight; TR, tricuspid regurgitant

Variable	**Cardiac Group (n = 22)**	**Respiratory Group (n = 13)**	**P value**
Age (years)	10.82 ±2.84	9.25 ±3.68	0.167
Sex (Male / Female)	9/ 13	7/ 6	0.503
Weight (kg)	7.8 (2.8 – 49.0)	8.4 (3.6 – 48.0)	0.149
Heart rate (bpm)	160 (100 - 250)	150 (100 - 190)	0.649
Respiratory rate (bpm)	60 (40 - 120) n=8	55 (30 – 80) n=21	0.228
Murmur (yes/no)	21/1	6/7	0.0017
Murmur grade	4 (0 – 6)	0 (0 – 5)	0.001
Systolic blood pressure (mmHg)	130.8 ±20.6 n=20	146.0 ±15.9 n=9	0.060
VHS	12.89 ±1.16	10.44 ±0.94	<0.001

LA:Ao (FOCUS)	2.1 (1.0 – 4.5)	1.1 (1.0 – 2.5)	<0.001
Pleural effusion (FOCUS) (yes/ no)	1/21	3/ 10	0.134
Pericardial effusion (FOCUS) (yes/ no)	1/21	0/ 13	>0.999
Left ventricular enlargement (yes/no) (FOCUS)	8/ 12	1/ 9	0.204
Right ventricular enlargement (yes/no) (FOCUS)	5/ 15	2/ 9	>0.999
LA:Ao (echocardiography)	2.3 ±0.5	1.3 ±0.4	<0.001
LVIDDN (cm/[kg$^{0.294}$])	2.13 ±0.41	1.29 ±0.32	<0.001
LVIDSN (cm/[kg0.315])	1.08 ±0.28	0.67 ±0.18	<0.001

Figure 1: Flow diagram illustrating the study protocol.

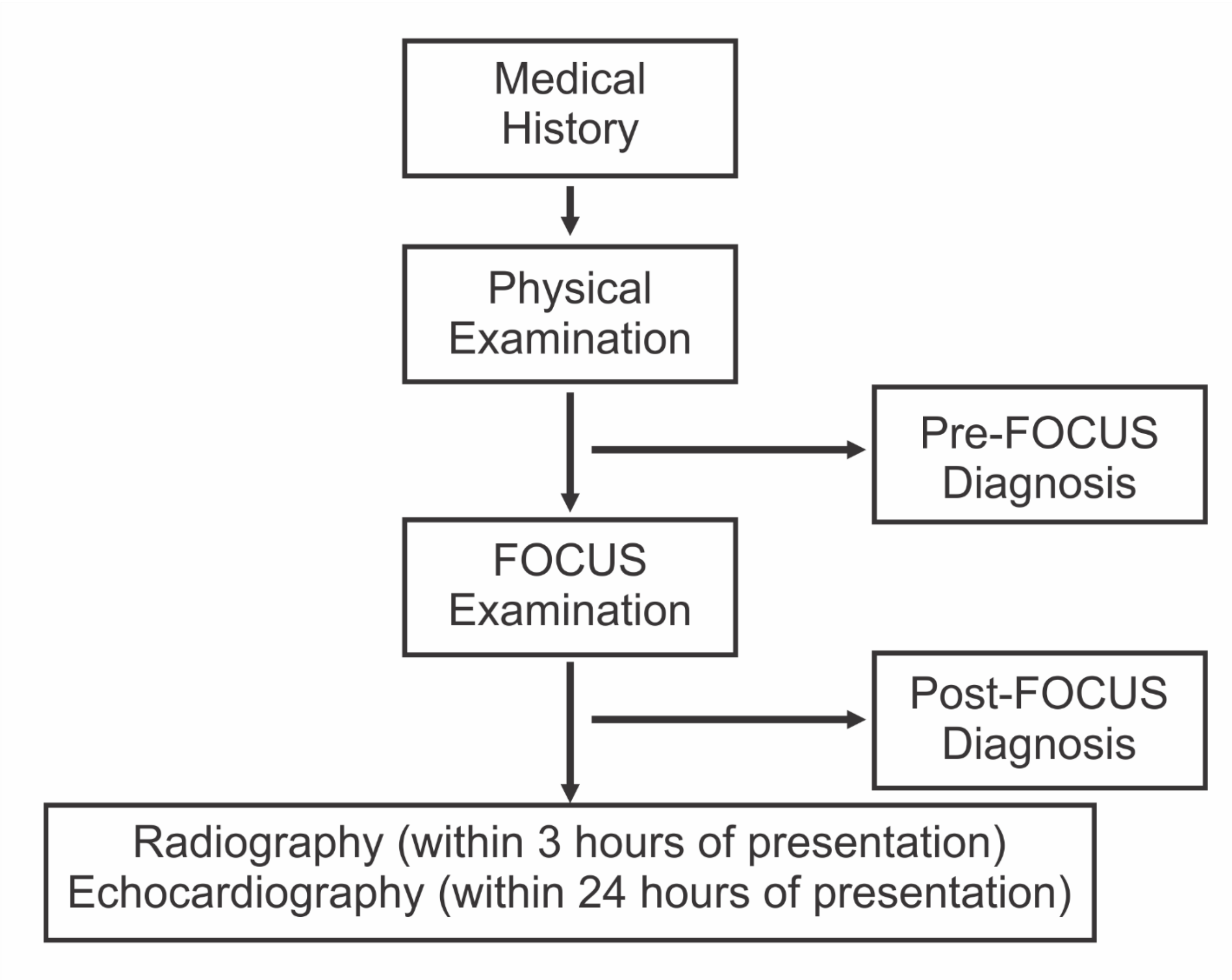

Figure 2: Flow diagram illustrating the numbers of dogs whose pre- and post-focused cardiac ultrasound (FOCUS) diagnosis by an emergency and critical care clinician agreed or disagreed with the reference diagnosis.